REMARKS/ARGUMENTS

Independent claims 1, 27, 38, and 51 have been amended for clarification to recite that the formulation is adapted for localized delivery to the lungs of a mammal via inhalation such that a reduced level of the hypertension reducing agent is absorbed into the systemic blood circulation and systemic effects are reduced. Claim 2 was also amended to recite localized delivery. Support for these amendments can be found at least on paragraphs [0011], [0012], and [0036] of the published application (i.e. U.S. Publication No. 2004/0265238). No new matter has been entered.

1. Currently Claimed Invention

As noted throughout the present specification, the present invention is premised, in part, on the known systemic hypertension reducing effects of ACEIs, ARBs, beta-blockers, calcium-channel blockers or vasodilators to treat pulmonary hypertension. However, the currently claimed formulations represent an improvement over conventional means for treating pulmonary hypertension, because the claimed formulations are adapted for localized delivery to the user's lungs such that a reduced amount of active is absorbed into the systemic blood circulation, as opposed to pure systemic delivery (e.g., absorbed into the systemic blood circulation and distributed to all parts of the body). As such, the currently claimed formulations can be administered in lower doses and reduce the level side effects associated with systemic delivery as known in the art.

For example, the present specification teaches that continuous intravenous administration (i.e., a purely systemic delivery) of prostacyclin results in significant side effects in patients, including jaw pain, nausea, and anorexia, plus the inconvenience and potential danger from prolonged cathertization and breakdowns in the delivery system. Further, because the agent is delivered systemically with only a small percentage of the agent actually absorbed by the pulmonary system, it must be administered in high dosages. See paragraph [0012].

The present specification also discloses that it has also been shown that calcium channel blockers may alleviate pulmonary vasoconstriction and prolong life in about 20 percent of patients with PPH. Rich S, Kaufmann E, Levy P S. The effect of high doses of calcium-channel

blockers on survival in primary pulmonary hypertension. N Engl J Med 1992;327:76-81. In patients who show evidence of an acute hemodynamic response, long-term treatment with calcium channel blockers administered orally can produce a sustained hemodynamic response and increase survival. However, such oral administration (i.e., pure systemic delivery) does not produce a localized effect on the lungs and therefore high doses must be administered producing a systemic effect and possibly associated side-effects. See paragraph [0014].

As noted above, the currently claimed invention is premised, in part, on the known systemic hypertension reducing effects of ACEIs, ARBs, beta-blockers, calcium-channel blockers or vasodilators to treat pulmonary hypertension. However, the currently claimed invention provides the benefit of localized delivery to the lungs of a patient. The localized effect achieved by the currently claimed formulations allows the use of reduced levels of active and reduces the side effects often associated with systemic delivery because less active is absorbed into the systemic blood circulation. Stated differently, the increased bioavailability of the present formulations can contain lower dosages of the hypertension-reducing agents while effectively treating pulmonary hypertension while also reducing the side-effects associated with treatment with these compounds.

2. Rejections under 35 U.S.C. §103

To establish a *prima facie* case of obviousness, according to a test predominately used by the courts, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim elements. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

With regard to the Supreme Court's decision in *KSR Int'l. Co. v. Teleflex, Inc.*, 550 U.S. ___, 82 USPQ2d 1385 (2007), it is noted that the Court did not dismiss the usefulness the well-

established "teaching, suggestion, or motivation" test set forth above, but merely cautioned against its rigid application. The Supreme Court in *KSR* commented that the Federal Circuit ' 'no doubt has applied the test in accord with these principles [set forth in *KSR*] in many cases.'' *Id.* at ___, 82 USPQ2d at 1396. However, the Supreme Court also opined that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. . ." *Id.* at ___, 82 USPQ2d at 1395-96. Regardless of the precise test used, the Court, quoting *In re Kahn*, cautioned that '' '[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.' '' *Id* . at ___, 82 USPQ2d at 1396.

A.

Claims 1-2, 12-16, 21, 25-30, 32, 34, 38-40, 51-54, 57-64, 66-69 and 71 stand rejected under 35 U.S.C. §103(a) as being obvious over U.S. Patent No. 5,554,610 to Williams et al (hereinafter "Williams") in view of U.S. Publication No. 2001/0031738 to Schwarz (hereinafter "Schwarz") and further in view of U.S. Patent No. 4,885,305 to Mead et al. (hereinafter "Mead"). Applicant respectfully traverses this rejection.

Applicant submits that none of the currently pending claims are obviated by Williams, Schwarz, Mead, or any combination thereof. For instance, each of the cited references, alone or in any combination, fail to teach, suggest, or render predictable all currently claimed elements. In particular, each of the cited references, alone or in any combination, fail to teach, suggest, or render predictable any of the following: (1) a formulation adapted for localized delivery to the lungs having a reduced concentration of a calcium channel blocker comprising about 0.001 to about 0.50 mg/ml; (2) a formulation adapted for localized delivery to the lungs such that a reduced level of the hypertension reducing agent is absorbed into the systemic blood circulation and systemic effects are reduced.

Williams is generally directed to methods of treating disorders associated with pulmonary hypertension by administering a given dose (mg) of a vasodilator, ganglion blocker, sympathetic nerve blocker or calcium channel blocker. Williams teaches that a "unit dose will normally

contain 0.01 to 50 mg for example 0.01 to 10 mg, of the Compound, or a pharmaceutically acceptable salt thereof. Unit doses will normally be administered once or more than once a day, for example 2, 3, or 4 times a day, more usually 1 to 3 times a day such that the total daily dose is normally in the range of 0.0001 to 1 mg/kg." See column 2, lines 20-29. Williams provides that such unit doses can be inhaled. The Office acknowledges that Williams does not disclose the recited pH levels, an isotonic formulation, or the addition of complexing agents.

Williams is silent regarding any concentration range of a calcium channel blocker, let alone a range specifically of 0.001 to 0.50 mg/ml as recited in currently amended independent claims 1, 27, 38, and 51. The daily dosage teaching of Williams, namely the administration of 0.0001 to 1 mg/kg per day includes a nearly infinite number of possible dosages, which in turn leads to an even greater number of potential concentrations. For instance, the lowest dosage range disclosed in Williams is 4 orders of magnitude lower than that of the highest dosage. Due to the breadth of such a teaching, Williams fails to provide any particular teaching that would provide the skilled artisan a reasonable basis for specifically selecting and preparing a formulation having the currently claimed concentration range from the nearly infinite possibilities referenced by Williams. For instance, when taken in 0.0001 increments (since this is the lower limit of Williams range), there are **10,000 different concentration** levels for one skilled in the art to select. Williams provides no teaching that would incite one skilled in the art to select any particular concentration range. As such, one skilled in the art would have no rational basis to select the currently claimed range from the nearly infinite possibilities encompassed within Williams. Additionally, the vast number of possibilities makes it impossible for one skilled in the art to experimentally try every possible (or even most) concentration. Therefore, Williams not teach, suggest or render predictable the claimed concentration range.

Furthermore, Williams fails to teach, suggest or render predictable a formulation adapted for localized delivery to the lungs such that a reduced level of the hypertension reducing agent is absorbed into the systemic blood circulation and systemic effects are reduced. Williams is silent about such formulation or that such formulations or methods of treatment can beneficially utilize a reduced level of active agent by avoiding the systemic circulation. Applicant notes that inhaled

snuffs or aerosols deposited in the throat, mouth, nasal mucosa, etc. can absorb into the systemic blood circulation system. Consequently, these formulations require an increased dosage of active agent since the drug will be transported throughout at least a section of the body prior to reaching the constricted arteries within the lung. As such, Williams not only fails to teach, suggest, or render predictable the currently claimed concentration range, but also the localized delivery of such a formulation to the lungs (i.e. lung vasculature).

As referenced above, Williams is silent regarding a formulation suitable for localized delivery to the lungs such that a systemic effect is circumvented (i.e. delivery such that systemic circulation is avoided prior to contacting the blood vessels connected to and within the lungs) as recited in independent claims 1, 27, 38 and 51. Similarly, Williams is silent regarding methods of treating pulmonary hypertension by locally delivering a calcium channel blockers to the lungs (i.e. to target the blood vessels connected and within the lung) of a patient. In light of this silence, the skilled artisan would have no basis to specifically targeting the deep lungs of a patient as opposed to the throat, mouth or nasal cavities. Additionally, in view of Williams extensive teachings related to elixirs, syrups and tablets, the skilled artisan would have no reasonable basis for modifying the teachings of Williams to avoid systemic absorption by targeting the deep lungs of a patient of depositing a calcium channel blocker. For instance, the elixirs, syrups and tablets taught by Williams certainly cannot be used for localized delivery to the lungs as currently claimed. Accordingly, Williams does not teach, suggest, or render predictable all elements of the currently claimed invention.

The Office cites Schwarz for support that it is well known in the art to utilize an isotonic formulation having a pH from 3 to 8 for formulations suitable for inhalation or nasal administration. Schwarz is directed to formulations for inhibiting endothelial-monocyte activating polypeptide II (EMAP II) by administering a compound that "inhibits EMAP II activity, including compounds that specifically bind to EMAP II (e.g., an antibody), compounds that downregulate EMAP II expression (e.g., an antisense oligonucleotide), or EMAP II receptor antagonists." Schwarz teaches that the compositions can be made isotonic and a pH of around 6. The Office relies on Mead for teaching a complexing agent.

Schwarz and Mead, however, each fail to cure the deficiencies of Williams discussed above.

Since Williams, Schwarz, Mead or any combination thereof all suffer from the same deficiencies, the cited references alone or in any combination fail to teach, suggest, or render predictable all of the currently claimed elements. Applicant submits that the Office has not established a *prima facie* case of obviousness. Therefore, Applicant submits that this rejection has been overcome and requests withdrawal of this rejection.

B.

Claims 1-2, 12-16, 21, 25-30, 32, 34, 38-40, 51-54, 57-64, 66-69 and 71 stand rejected under 35 U.S.C. §103(a) as being obvious over U.S. Patent No. 4,885,305 to Kiechel et al. (hereinafter "Kiechel") in view of Williams and further in view of Mead. Applicant respectfully traverses this rejection.

Applicant submits that none of the currently pending claims are obviated by Kiechel, Williams, Mead, or any combination thereof. For instance, Applicants submit that the combination of Kiechel and Williams in the manner proposed is improper. Additionally, each of the cited references, alone or in any combination, fail to teach, suggest, or render predictable all currently claimed elements. In particular, each of the cited references, alone or in any combination, fail to teach, suggest, or render predictable any of the following: (1) a formulation adapted for localized delivery to the lungs having a reduced concentration of a calcium channel blocker comprising about 0.001 to about 0.50 mg/ml; (2) a formulation adapted for localized delivery to the lungs such that a reduced level of the hypertension reducing agent is absorbed into the systemic blood circulation and systemic effects are reduced.

Kiechel is directed to a nasal pharmaceutical composition adapted to be "absorbed **systemically through the nasal mucus**" to treat hypertension. See abstract. The compositions include "calcium antagonists, also called calcium channel blocking agents." See column 1, lines 11-12. Preferred calcium antagonists include "1,4-dihydro-4-phenylpyridines such as Bay k 9320, felodipine, fluordipine, FR 7534, FR 34 235, FR 38 245, mesudipine, nicardipine, nifedipine, niludipine, nimodipine, nisoldipine, nitrendipine and SKF 24 260." See column 1,

lines 60-64. "Suitable concentrations of active agent are for example about 0.1 to about 0.45% (i.e. 1 to 4.5 mg/ml)." See column 3, lines 44-46. Kiechel teaches that "up till now the calcium antagonists of the invention have not been administered **systemically by nasal route** for therapy for diseases." See column 1, lines 34-36. Kiechel teaches that "anatogonists ... are rapidly **absorbed from the nasal mucus into the systemic blood circulation** without significant first pass effect." See column 4, lines 38-40. As such, Keichel clearly teaches the benefits of administration of calcium antagonists systemically through the nasal mucus membranes.

However, Kiechel is silent regarding a formulation including a concentration of a calcium channel blocker comprising about 0.001 to about 0.50 mg/ml. **This is not surprising considering Kiechel teaches a formulation for absorption through the nasal mucus into the systemic blood circulation. As such, the Kiechel formulations require a concentration range greater than the currently recited concentration range.** More specifically, Keichel only teaches the absorption into the systemic circulatory system. As understood by one skilled in the art, the systemic circulation carries oxygenated blood away from the heart, the extremities of the body, and returns deoxygenated blood back to the heart. Thus, drug delivery to the systemic circulatory system, as taught in Kiechel, results in the drug traveling throughout the body prior to reaching the lung vasculature. As such, the Kiechel formulations and methods of treatment necessarily require increased levels of an active agent due to the indirect route of reaching the lung vasculature.

Contrary to the teachings of Kiechel, the currently claimed formulations (and methods of treatment) are adapted for localized delivery to the lungs such that systemic effects are reduced as recited in each independent claim. For instance, pulmonary hypertension is related to the vasoconstriction or tightening of blood vessels connected to and within the lung. Such a constriction makes pumping blood through these vessels more difficult. Over time, this condition increases the blood pressure in vessels within the lungs and the pulmonary artery. Since the currently claimed formulations are adapted for localized delivery to the affected areas, **a reduced level of active agent is required for treatment**. Accordingly, the currently claimed invention provides formulations and methods of treatment which largely circumvent the systemic blood flow and thus largely **circumvent systemic side effects associated with systemic**

absorption as taught by Kiechel. Contrary to the explicit teachings of Kiechel, the currently claimed formulations and methods of treatment target the blood vessels connected to and within the lungs. These blood vessels return blood back to the heart and are known to be part of the pulmonary circulation as opposed to the systemic circulation.

Williams is generally directed to methods of treating disorders associated with pulmonary hypertension by administering a given dose (mg) of a vasodilator, ganglion blocker, sympathetic nerve blocker or calcium channel blocker. Williams teaches that a "unit dose will normally contain 0.01 to 50 mg for example 0.01 to 10 mg, of the Compound, or a pharmaceutically acceptable salt thereof. Unit doses will normally be administered once or more than once a day, for example 2, 3, or 4 times a day, more usually 1 to 3 times a day such that the total daily dose is normally in the range of 0.0001 to 1 mg/kg." See column 2, lines 20-29. Williams provides that such unit doses can be inhaled. The Office acknowledges that Williams does not disclose the recited pH levels, an isotonic formulation, or the addition of complexing agents.

(1) No rational basis modifying Kiechel by Williams

Applicant notes that the Office appears to be citing Williams for teaching the currently claimed concentration range of 0.001 mg/ml to about 0.50 mg/ml and arguing that one skilled in the art would have a reasonable basis for modifying the nasal formulations (having an increased amount of active) specifically by employing the allegedly taught reduced concentration range (which Applicant does not admit) of Williams. As discussed above, however, Kiechel explicitly and only teaches the administration of active through the nasal mucosa for absorption into the systemic blood flow. Consequently, the formulations and methods of Kiechel require an increased concentration of active ingredient because the active is carried throughout the systemic blood flow prior to reaching the desired area of treatment, namely the blood vessels connected to and within the lungs. As such, one skilled in the art would readily recognize that if the nasal formulations and methods of treatment taught by Kiechel were modified (for some reason) to include the currently claimed concentration range as allegedly taught by Williams (which Applicant does not admit) then the modified-Keichel formulations and methods would largely be devoid of any therapeutic impact while undesirably still promoting systemic effects. Accordingly, one skilled in the art would have no rational basis for modifying Kiechel in the

manner suggested. Furthermore, such a modification would likely render the Kiechel formulations unfit for their intended purpose. That is, by reducing the concentration in the active the targeted areas will likely not receive a therapeutic amount (if any at all) of active, thus, rendering them useless. Applicants again note that Kiechel's formulations require greater concentrations of active because they are adapted specifically for absorption into the systemic blood circulation.

For at least this reason, Applicant submits that the proposed modification/combination is improper. As such, Applicant submits that this rejection has been overcome and request withdrawal of this rejection.

(2) Each of the cited references, individually or in any combination, do not teach, suggest, or render predictable each and every claimed element

Since neither Kiechel nor Williams teach, suggest, or render predictable, an inhalable formulation for the treatment of pulmonary hypertension including a complexing agent, the Office relies on Mead for curing the common deficiency of Kiechel and Williams. Mead is directed to compositions including anticholinergics and endothelin antagonists that exhibit a synergistic effect in the treatment of respiratory tract diseases. Anticholinergics are a class of medications that inhibit parasympathetic nerve impulses by selectively blocking the binding of the neurotransmitter acetylcholine to its receptor in nerve cells. Endothelin antagonists block endothelin, a 21-amino acid vasoconstricting peptide produced primarily in the endothelium. Mead teaches that such compositions can be used for the treatment of pulmonary hypertension. See column 2, line 61. The compositions may be provided in the form of a propellant-free inhalable solution or suspension, wherein the solvent may be aqueous or alcoholic. See column 8, lines 64-67.

However, Mead does not cure the deficiencies of Kiechel, Williams, or any combination thereof. For instance, Mead is completely silent regarding calcium channel blockers. As such, Mead necessarily fails to teach, suggest, or render predictable a formulation having a particular concentration of a calcium channel blocker comprising about 0.001 to about 0.50 mg/ml. Since Kiechel and Mead both fail to teach, suggest, or render predictable the currently claimed concentration range of a calcium channel blocker, the combination of these references also fails

to teach, suggest, or render predictable the claimed concentration range as recited in each independent claim. Accordingly, any combination of Kiechel, Williams and Mead does not teach, suggest, ore render predictable all claimed elements as recited in independent claims 1, 27, 38 and 51 (or any claims dependent thereon). Therefore, the combination of Kiechel, Williams, and Mead does not establish a *prima facie* case obviousness. Applicant requests withdrawal of this rejection.

Since Kiechel, Williams, and Mead, alone or in any combination, fail to teach, suggest or render predictable any of the following: (1) a formulation adapted for localized delivery to the lungs having a reduced concentration of a calcium channel blocker comprising about 0.001 to about 0.50 mg/ml; (2) a formulation adapted for localized delivery to the lungs such that a reduced level of the hypertension reducing agent is absorbed into the systemic blood circulation and systemic effects are reduced and the combination of Kiechel and Williams is improper, none of the currently pending claims are obviated. Applicant requests withdrawal of this rejection.

C.

Claim 71 stands rejected under 35 U.S.C. §103(a) as being obvious over Williams in view of Schwarz in view of Mead and further in view of U.S. Patent No. 5,804,212 to Illum (herinafter "Illum"). Applicant respectfully traverses this rejection. The Office cites Illum for teaching a lecithin.

Illum is directed to nasal formulations (not adapted for localized delivery to the lungs) including microspheres. These formulation are administerd to the nasal cavity for delivery of drugs that will act within the systemic blood circulation (contrary to the currently claimed invention).

In this regard, and as previously discussed, all currently pending claims, are not obviated by Kiechel, Williams and Schwarz, either separately or in combination, and Illum does not remedy any of the noted deficiencies in this regard. Applicant thus submits that these rejections have been overcome and requests withdrawal thereof.

Provisional Double Patenting Rejection

Claims 1, 2, 12-16, 21, 25-30, 32, 38-40 and 51-71 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting of copending application Serial No. 11/316,458. Since this is a provisional rejection and the Office has not indicated the allowance of any of the pending claims, Applicant will not file a terminal disclaimer at this time. Upon indication of allowable subject matter, Applicant will submit a terminal disclaimer to overcome the rejection.

Conclusion

In view of the amendments and remarks made above, Applicant submits that the pending claims are now in condition for allowance. Applicant respectfully requests that the claims be allowed to issue. If the Examiner wishes to discuss the application or the comments herein, the Examiner is urged to contact the undersigned by telephone.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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